

Overview of the Chemical Science and Technology Laboratory and its Strategic Planning Process

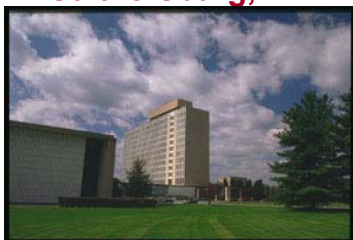


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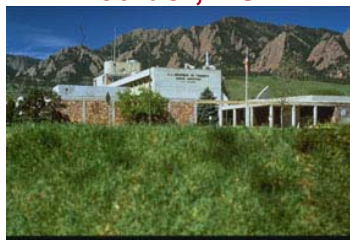
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CSTL research and service activities occupy two campuses...

Gaithersburg, MD



Boulder, CO



...and take place in two joint Institutes

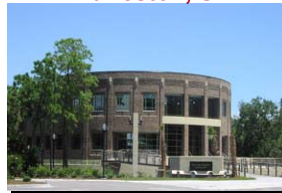
CARB

University of Maryland



HML

Charleston, SC



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Topics to be Discussed

- CSTL: Who We Are and What We Do
- How We Balance Research and Delivery of Measurement Services
- How We Set Priorities
- How We Maintain the Flexibility to Respond to Urgent National Needs That Arise
- How We Balance the “Old” with the “New”
- How Do We Connect With Other NMIs to Address U.S. Industry’s Global Needs

NIST Mission

*To promote U.S. **innovation** and **industrial competitiveness** by advancing **measurement science, standards, and technology** – in ways that enhance economic security and improve the quality of life for all Americans.*

- *NIST is well positioned – at the nexus of science and industry – to advance this mission in support of industry and national needs.*

The Chemical Science and Technology Laboratory ...

... fulfills the NIST Mission

in the areas broadly encompassed by chemistry, the biosciences, and chemical engineering

by addressing customer needs for measurements, standards, data, and assessment of new technologies

CSTL Operational Strategy

We carry out our mission by engaging in three primary activities:

- **Standards Development and Deployment**

- Provide “higher order” reference materials, data, and calibrations to increase transactional efficiency in trade and to facilitate regulatory compliance both domestically and internationally
- Develop advanced procedures and protocols to increase access and dissemination of chemical, biochemical and physical property data, and facilitate data exchange

- **Technology Development, Assessment and Deployment**

- Assess new chemical, biological or physical measurement technologies to facilitate their acceptance in the marketplace and/or regulatory community
- Take advantage of recent scientific advances to develop new tools for measurement service delivery

- **Measurement Science**

- Conduct research in measurement science to:
 - enable NIST to address next generation standards and data needs, and
 - underpin the development, implementation and/or assessment of new technologies.
 - elucidate and quantify the fundamental physical and chemical properties of chemical and biological materials
- Approach absolute metrology by reducing uncertainties and bias in physical and chemical measurements
- Facilitate physical and chemical characterization of materials at the nano to molecular scale
- Develop and validate chemical, biochemical, and physical property models both at the molecular and systems level

CSTL at NIST – Past and Present

Early 1900's

Division I

Heat and Thermometry

“As primary standards, this section had acquired a number of specially constructed ... thermometers in Europe and was prepared to **certify almost any precision thermometers used in scientific work, industrial and commercial thermometers.**”

Division III

Chemistry

“This section was increasingly involved in its investigation of properties for the Government testing program and produced **standard samples of alloys, steels, iron ores, copper slags, cements, and lubricating oil.**”



SING STAR, MONDAY, MARCH 11, 1901

CORRECT MEASURES

Function of the New Bureau of Standards.

LABORATORY TO BE DIRECTED

tail's Need of Establishment.

A HANDICAP REMOVED

A new bureau of the government, authorized by the last Congress, will be established in this city in the near future and will give employment to a number of persons. It is to be known as the national bureau of standards and is to be under the control of the Treasury Department. A separate building for a laboratory, to cost not to exceed \$250,000, is to be erected on a site to be purchased at a cost of \$25,000. Mr. Samuel W. Stratton of Chicago has

Early 2000's

CSTL

Measurements and Standards for:

- Healthcare
- Food Safety and Nutrition
- Materials Characterization at the Nanoscale
- Genomics, Proteomics, and Cellular Measurements
- Chemical Sensing and Imaging Technologies

CSTL supports NIST's Mission by addressing customer needs for **measurements, standards, and data** in the areas broadly encompassed by **chemistry, the biosciences, and chemical engineering**

Chemical and Physical Measurement Competencies

World-Class Metrologically-Based
Competencies and Measurement Capabilities

Internationally Vetted and Recognized

Measurement Services provided to Customers

- SRMs™ and NTRMsSM
- SRD
- Calibration Services
- Reference Methods [disseminated via publications, etc.]
- Testing Services [for selected high priority needs]
- Services to Other State and Federal Agencies

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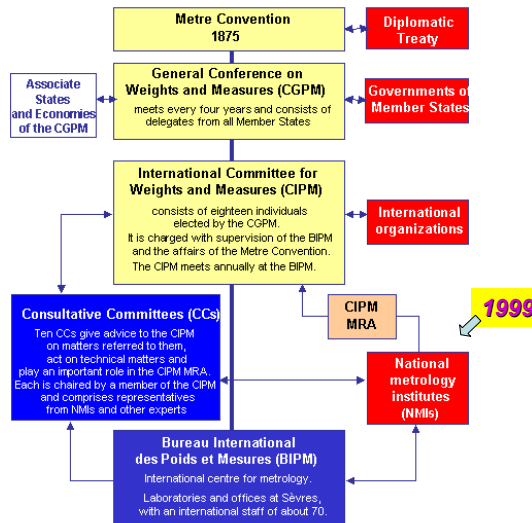
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Metre Convention, CIPM MRA ...

The CIPM MRA provides an open, transparent, and comprehensive system for vetting the calibration and measurement capabilities that underpin services that we deliver to customers.



We can no longer ask customers to “trust us, we’re from NIST” !!!

Mutual Recognition Arrangement (MRA) developed by the CIPM



- **Signed by: 38 NMI Directors in October 1999**; has **now** been signed **by** representatives of **67 institutes** (45 Member States, 20 Associates, 2 international organizations) and covers a further 113 institutes designated by the signatory or other appropriate official bodies for specific services that they do not deliver themselves.
- **Requires:**
 1. Declaring and documenting calibration and measurement capabilities (CMCs)
 2. Evidence of *successful* participation in formal, *relevant* international comparisons
 3. Demonstration of system for assuring quality of each NMI's measurement services

Traceability to stated references and global confidence in this realization are the basis for mutual recognition and confidence in data used to facilitate and underpin international trade and decisions regarding health, safety, commerce, and scientific studies

Addressing MRA Requirements for CSTL's Physical Measurement Services

CSTL has CMCs for Flow (14), Temperature and Humidity (99), Vacuum and Pressure (23)

- are members or leaders in CCT and CCM
- is responsible for the International Temperature Scale, and its implementation, in the US
- has participated or led International Comparisons for physical measurements since 1920.

Temperature (from 0.65K to 1235K)

- Resistance Thermometers
- Fixed point cells
- Thermocouples
- Radiation Thermometers
- Liquid in Glass Thermometers
- Pyrometers

Humidity (from ppb to 100%)

- Hydrometers

Liquid Volume (3.8 L to 7600 L)

- Gravimetry

Pressure and Vacuum (10^{-7} to 10^8 Pa)

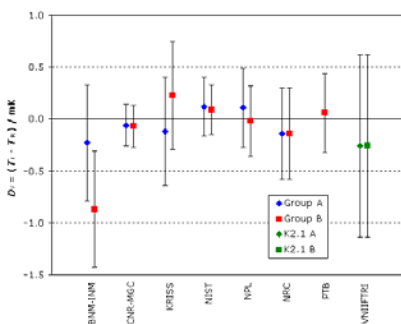
- Piston gages
- Spinning rotor gages
- Ionization gages
- Leak rates
- Low pressure gages

Flow

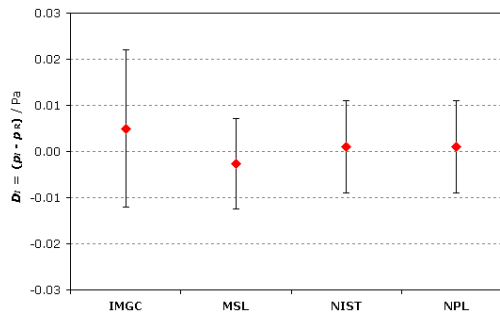
- Flow meters – Gas, Liquid
- Anemometer – Gas flow speed
- Low gas flow rates (10^{-13} to 10^{-3})

Evidence of successful participation in formal, relevant Key comparisons:

CCT K2 - Comparison of Capsule-type Standard Platinum Resistance Thermometers (CSPRT) 234.3156 K, the triple point of mercury on ITS-90



CCM.P-K5 Differential pressure, nominal value 3 Pa



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MRA requirements for CSTL's Chemical Measurement Services

CSTL has declared over 1100 NIST CMCs for Chemical Measurements are included in the ~3500 Chemistry CMCs published in the CIPM MRA Appendix C.

- | | | |
|--|--|--|
| <p>1 High Purity Chemicals</p> <p>1.1 Inorganic Compounds</p> <p>1.2 Organic Compounds</p> <p>1.3 Metals</p> <p>1.4 Isotopics</p> <p>1.5 Other</p> <p>2 Inorganic Solutions</p> <p>2.1 Elemental</p> <p>2.2 Anionic</p> <p>2.3 Other</p> <p>3 Organic Solutions</p> <p>3.1 PAHs</p> <p>3.2 PCBs</p> <p>3.3 Pesticides</p> <p>3.4 Other</p> <p>4 Gases</p> <p>4.1 High Purity</p> <p>4.2 Environmental</p> <p>4.3 Fuel</p> <p>4.4 Forensic</p> <p>4.5 Medical</p> <p>4.6 Other</p> <p>5 Water</p> <p>5.1 Fresh Water</p> <p>5.2 Contaminated Water</p> <p>5.3 Sea Water</p> <p>5.4 Other</p> | <p>6 pH</p> <p>7 Electrolytic Conductivity</p> <p>8 Metals and Metal Alloys</p> <p>8.1 Ferrous Metals</p> <p>8.2 Non-Ferrous Metals</p> <p>8.3 Precious Metals</p> <p>8.4 Other</p> <p>9 Advanced Materials</p> <p>9.1 Semiconductors</p> <p>9.2 Superconductors</p> <p>9.3 Polymers and Plastics</p> <p>9.4 Ceramics</p> <p>9.5 Other</p> <p>10 Biological Fluids and Materials</p> <p>10.1 Blood, Plasma, Serum</p> <p>10.2 Urine Fluids</p> <p>10.3 Hair</p> <p>10.4 Tissues</p> <p>10.5 Bone</p> <p>10.6 Botanical Materials</p> <p>10.7 Other</p> <p>11 Food</p> <p>11.1 Nutritional Constituents</p> <p>11.2 Contaminants</p> <p>11.3 GMOs</p> <p>11.4 Other</p> | <p>12 Fuels</p> <p>12.1 Coal and Coke</p> <p>12.2 Petroleum Products</p> <p>12.3 Bio-mass</p> <p>12.4 Other</p> <p>13 Sediments, Soils, Ores, and Particulates</p> <p>13.1 Sediments</p> <p>13.2 Soils</p> <p>13.3 Ores</p> <p>13.4 Particulates</p> <p>13.5 Other</p> <p>14 Other Materials</p> <p>14.1 Cements</p> <p>14.2 Paints</p> <p>14.3 Textiles</p> <p>14.4 Glasses</p> <p>14.5 Thin Films</p> <p>14.6 Coatings</p> <p>14.7 Insulating Materials</p> <p>14.8 Rubber</p> <p>14.9 Adhesives</p> <p>14.10 Other</p> <p>15 Optical Properties</p> |
|--|--|--|

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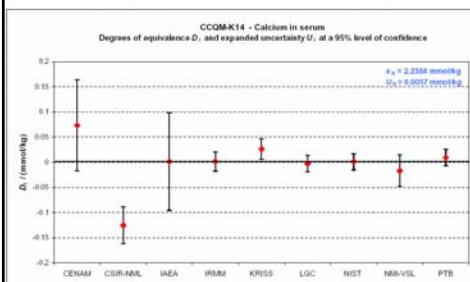
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Evidence of successful participation in formal, relevant Key comparisons:

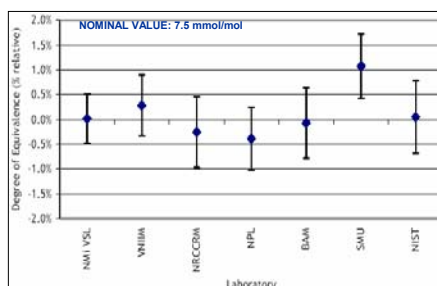
- Providing leadership and successfully participated in ~ 80 CCQM comparisons to meet requirements of MRA during the past five years;
 - Coordinating Laboratory for ~ 40 studies

Recent Examples:

CCQM-K14: Calcium in Serum



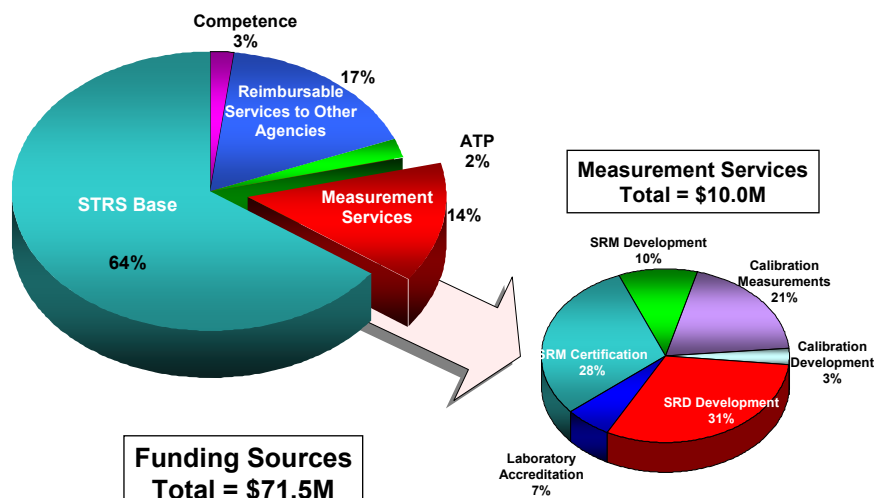
CCQM-16: Gas mixtures - Natural Gas Type IV – ethane (1 of 12 measurands) (low calorific mixture)



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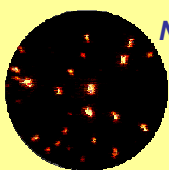
CSTL Funding, FY2006 est.



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Since the early 1970's, CSTL has Provided Measurement Support for Homeland Security Applications



Nuclear

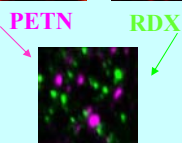
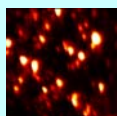
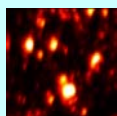


- Support IAEA SIMS standards efforts in their environmental sampling requirements

Particles on substrate identified by ^{235}U and ^{238}U SIMS signals. Field of view is about 150 micrometers

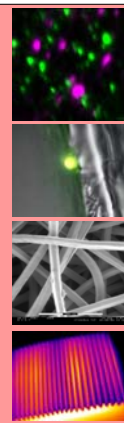
POST 9-11

- Environmental Hi-EX measurement capability and standards



TODAY

- Particle release from surfaces
- Efficiency of explosive particle transport and collection
- Temperature programmed desorption of explosives particles
- Characterization of vapor collection on mesh surfaces
- Explosive particle standards

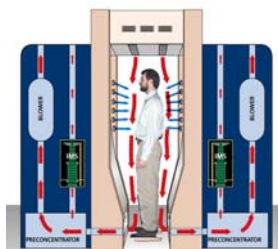


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Currently Collaborating with the Transportation Security Agency in Assessing New Human Entry Security Portal Technologies

Goals:

- Use advanced surface analysis tools to study the performance characteristics of trace explosive detection portals.
- Improve sensitivity, collection efficiency and reduce number of false positives.



Trace Explosive Detection Portal

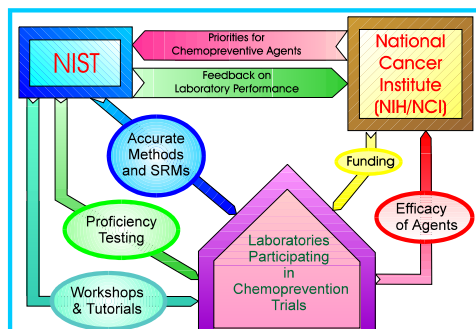


Tabletop Trace Explosive Detection Unit

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From the late 1980's to the late 1990's NIST provided measurement QA Support for NCI Cancer Chemoprevention Studies



Project Description: NIST provided proficiency testing samples, SRMs, methodologic development and assistance, and workshops to laboratories conducting chemoprevention trials.

Results: Interlaboratory comparability for measurements of vitamins, carotenoids, and other agents in human serum and food materials have substantially improved.

Relevance: Results of chemoprevention trials from participating laboratories are more comparable, leading to more definitive conclusions about the efficacy of potential agents.

Current Partnerships with NCI/NIH

- QA for NCI Early Cancer Detection Research Network
- QA for NCI \$100M/yr. Clinical Proteomics Program
- SRMs for Dietary Supplements; Value-assigned for
 - Active compounds in botanical supplements
 - Vitamins and micronutrients
 - Contaminants (e.g., pesticides and toxic metals)
- SRMs to provide measurement QA for studies for assessing the nutritional status of the U.S. population
- Reference Methods and SRMs to provide support NIH Metabolomics Roadmap Investigators

Other CSTL Products and Measurement Services

- **Measurement Research**
~350 publications/year
- **Standard Reference Materials**
~ 25,000 units sold/year
- **Calibrations and Tests**
~1000 items calibrated/year
- **Standard Reference Data**
~650 units sold/ year



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NIST Standards for Chemical Measurements

Chemical standards constitute **over 2/3** of ~1,400 NIST SRM types, and **~26,500** of over 32,000 NIST SRM Units sold in FY05

- High Purity Neat Chemicals
- Organic Solution Standards
- Inorganic Solution Standards
- Gas Mixture Standards
- Isotopic Standards

- **Complex Matrix Standards**
 - Advanced Materials
 - Biological Fluids/Tissues
 - Foods/Botanicals
 - Geologicals
 - Metals and Metal Alloys
 - Petroleum/Fossil Fuels
 - Sediments/Soils/Particulates
 - Cements

- **Molecular Spectrometry Standards**
- **Electrolytic Conductivity Standards**
- **pH / Ion Activity Standards**

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CSTL Standards for Physical Measurements

Mechanical Measurements

Hydrometers
Liquid Density and Volume
Flow (gas, water, HC)
Airspeed Instruments



CSTL performs about 50% of all NIST calibrations for physical measurements, and serves ~ 150 companies each year

Thermodynamic Quantities

Pressure
Vacuum, Low Pressure, and Leak
Lab- and Industrial-grade Thermometers
Thermocouples, TC materials
Resistance Thermometry
Humidity



Standard Reference Data

- Thermodynamics data such as TRC
- Fluids Properties data
- Kinetics data
- WebBook for Chemical Properties data
- Computational Chemistry Database
- Mass Spectral Data
- Other spectral data such as FTIR



New Approaches

- Guided Data Capture (TRC)
- Expanded web-based dissemination
- IUPAC Standard Chemical Identifier
- Traceability through Reference Data

CSTL is a prominent source of SRD products at NIST.

- ~ 4000 Mass Spectral Databases sold each year through distributors
- > 350 Thermodynamics Research Center publications are distributed annually
- ~650 units of CSTL databases were distributed directly to customers.
- > 800,000 customers served via the web

Many CSTL products such as AMDIS, dynamic link libraries, fluid property coefficients, and source code portions were incorporated into commercial software packages.

We Provide Services to High Technology Industries ...

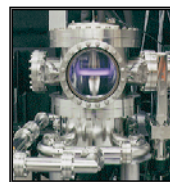
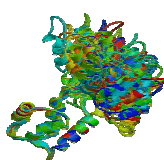


Aerospace and Transportation

- Standards for low NO emissions from vehicles
- Thermophysical data on rocket propellants
- Cryogenic measurements for NASA's future space vehicles
- Properties of aircraft fire suppressants

Semiconductors

- SRMs for measuring P, As, and B in Si
- Thermometry and plasma process monitoring in semiconductor fabrication
- Electrical carrier density measurements
- Neutron transmutation in semiconductor doping



Biotechnology

- Proteomics
- DNA diagnostics
- Human identification
- Tissue engineering

... and Mature Industries



Chemical Processing

- Chemistry WebBook, MS Database, IR Database
- Thermal/physical properties of fluids, refrigerants, ionic liquids
- Molecular property data for chlorinated hydrocarbons
- Zeolite reference materials

Health and Food

- Reference methods and SRMs for clinical markers
- Methods and SRMs for dietary supplement safety
- Nutritional composition SRMs
- Environmental contamination SRMs



Energy

- SRMs for low-sulfur fuels
- Natural gas flow and composition standards
- Gas solubilities in steam for power generation

Constantly Balancing the “Old” with the “New”

SRM 1d - Argillaceous Limestone

Versions of SRM 1 have been provided since 1910.

Limestone is critical to the building industry and also in the manufacture of lime for the agricultural and chemical industries.



SRM 2399 - Fragile X (DNA Triplet Repeat) Standard

And we support emerging industries and genetic testing laboratories in accurately counting fragile-X repeat sequences, NIST has developed a new reference material that can be used as a check on test procedures and for quality control. SRM 2399 consists of nine samples of DNA measured and certified by NIST for triplet repeats ranging from 20 to 118. **The triplet repeat standard joins more than 50 reference materials produced by NIST for quality control in clinical testing.**



Areas of Increasing Emphasis

- Genomics/Gene Expression, Proteomics, metabolomics and Cellular Measurements
- Functional Foods and Dietary Supplements
- Virtual Measurements to Fill in Critical Information Gaps
- NanoMetrology and NanoManufacturing
- Measurements and Standards for Process Certification

*While maintaining the flexibility to rapidly respond to
National needs in a timely fashion*



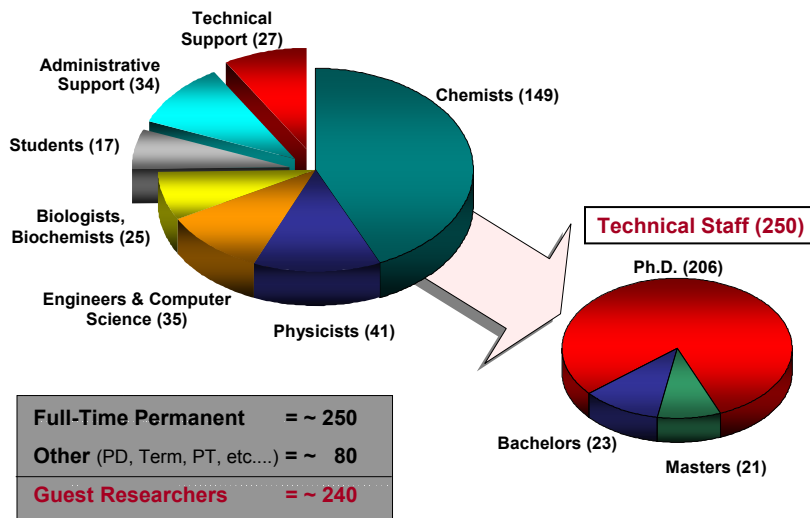
How are we keeping *our* priorities straight –

Are we on the proper course ???

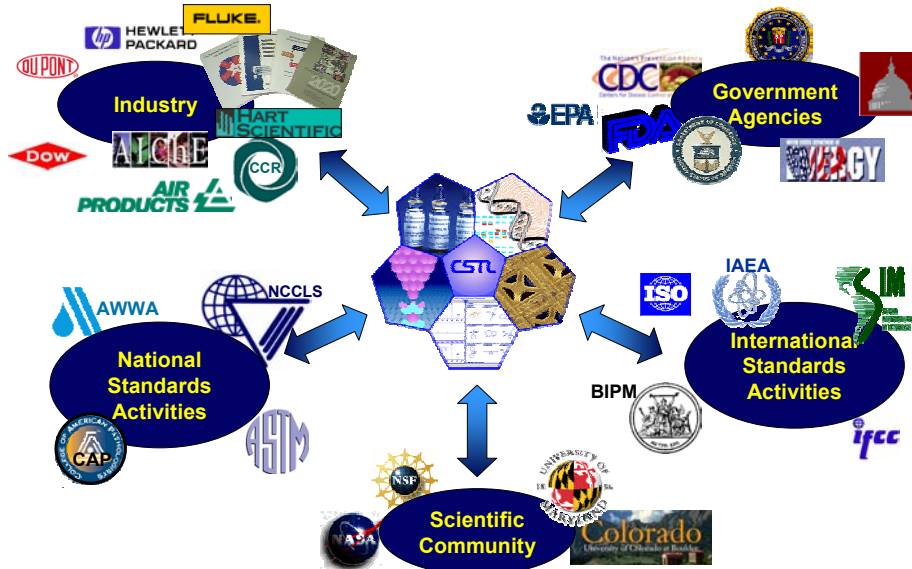


How we are managing *our* load?

CSTL Staff



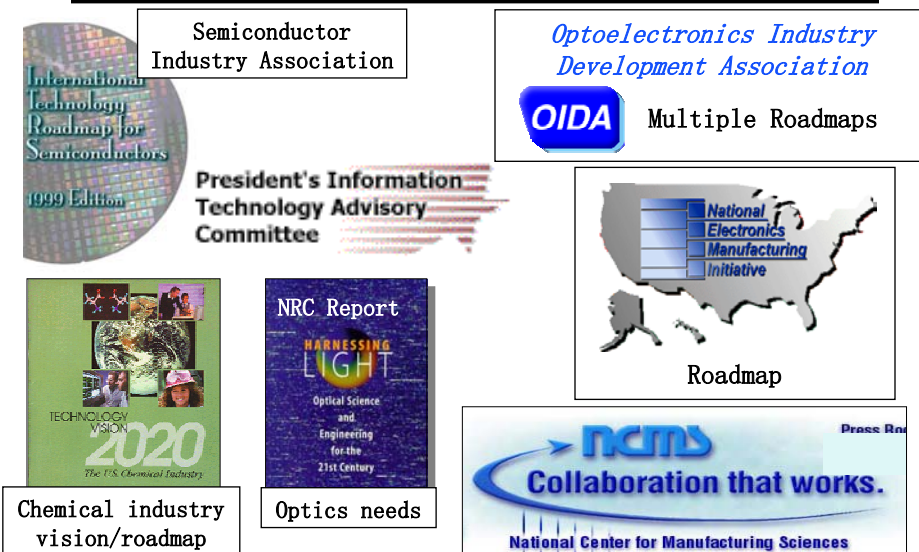
Direction of CSTL Programs Determined by Interactions with Stakeholders



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Programs also Guided by Stakeholder Roadmaps and Needs Assessment



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Measurements for Biotechnology

www.mfbprog.org.uk

Better Measurements for Biotechnology



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Gene measurement

Many thousands of DNA measurements are made daily across a wide range of sectors and applications, but how reliable are they? MfB works to make DNA measurements more comparable and to make quantification more certain.

MfB projects tackle:

- International standards and performance indicators for DNA measurement
- A primary method for DNA quantification
- Standard units for gene expression
- Specificity standards and performance indicators for microarrays
- Comparability and consistency of DNA measurements
- Critical data analysis for trace DNA measurements
- Standardisation requirements for SNP genotyping

Protein measurement

Protein populations, structures and interactions hold the key to major prizes for biotechnology, but present enormous challenges in measurement. Increased confidence in analysing complex protein mixtures will benefit drug discovery, disease diagnosis and wider applications of biotechnology in food, agriculture and the environment.

MfB projects tackle:

- Validated procedures and reference standards for more confident separation, quantification and identification of complex protein mixtures
- More comparable measurement of higher order structure and interactions of proteins

Cell-based technology

Cell-based tests are vital tools in drug discovery and could reduce animal testing, but confidence in them needs to be increased. The key need is assurance of the cells' fitness for use.

MfB projects tackle:

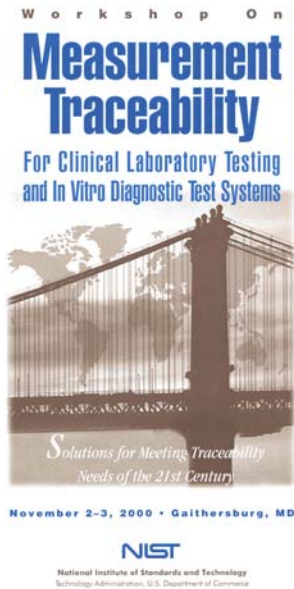
- A systematic approach to identifying and ameliorating the sources of variability in cell-based tests
- Targeted development and validation of biomarkers for the cell-based modelling of complex biological processes
- Developing quality metrics for validating and standardising toxicogenic, array-based measurements

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... and NIST-convened Workshops as needed



Attendees included:

- IVD Manufacturers
- Regulatory Agencies and Notified Bodies
- Providers of Proficiency Testing Programs, Laboratory Accreditation, and Measurement Quality assessment Materials
- Laboratory professionals involved in standardization of laboratory methods
- International Standards Laboratories



“.... the traceability of values assigned to calibrators and control materials must be assured through available reference measurement procedures and/or reference materials of a higher order ...”

EC-IVD Directive Annex 1 (3)

US IVD Manufacturers requested that NIST assist them in meeting new EU IVD Directive measurement traceability requirements

Approximately 60 % of the in vitro diagnostic medical devices (IVD MD) currently on the ~ \$6 B/yr European market are imported from the US. (Worldwide, the in vitro diagnostic device market is ~\$20B)

CSTL RESPONSE:

- Held Industry Driven IVD Workshop at NIST in November 2000
- Helped organize follow-on Workshop held at BIPM, France in June 2002 that led to the creation of the Joint Committee on Traceability in Laboratory Medicine
- Webcast Workshop on Uncertainty in Clinical Measurements, March 2003
- Continuing updates with Industry at AACC National Meetings
- Actively participating in ISO Technical Committees and other global standards development organizations.

Joint Committee on Traceability in Laboratory Medicine (JCTLM)



A global body, established in Paris on 12 June 2002, to meet the need for a worldwide platform to promote and give guidance on internationally recognized and accepted equivalence of measurements in Laboratory Medicine and traceability to appropriate measurement standards.

The Declaration of Cooperation between the International Committee of Weights and Measures (**CIPM**), the International Federation for Clinical Chemistry and Laboratory Medicine (**IFCC**), and the International Laboratory Accreditation Cooperation (**ILAC**) for establishment of the **JCTLM** can be found at

<http://www.bipm.org/en/committees/jc/jctlm/declaration.html>

Another Example of International Regulations that Impact U.S. Industry

ISSUE: European Union member nations are about to restrict the use of hazardous substances in electrical and electronic products and components.

EU Directive 2002/95/EC, Restriction of Hazardous Substances (RoHS)

- Restricts **Cd, Pb, Hg, Cr6+, Flame retardants (PBBs, PBDEs)**
- Requires **manufacturers to implement testing procedures** for raw materials and finished products to ensure compliance with these mandates

China recently announced similar restrictions as part of their drive to reduce the problem of electronic waste in their country.

In **Japan**, electronics manufacturers recently set specifications to restrict the use of 24 substances by their suppliers and their own manufacturing facilities.

Many States in the US either have or are considering RoHS-like statutes

These regulations and specifications are aimed at products going to market.

RoHS is but one of many EU directives

- IVD MD
- Waste Electrical and Electronic Equipment
- Registration, Evaluation, and Authorization of Chemicals
- End-of-Life Vehicles
- Packaging Directive
- Integrated Product Policy
- Batteries Directive
- Energy-Using Products

Restricted Substances in Materials - Testing and Reporting Procedures Workshop

Workshop Date: October 5 – 7, 2005, NIST

Attendees: 127 (92 from industry; 1 each from 6 non-US countries)

Representing: Major electronics OEMs, small and medium size businesses (SMBs), independent testing labs, industry associations, standards developing organizations (SDOs)

Website: www.cstl.nist.gov/nist839/RoHS/RoHS_Meeting.htm

Workshop Presentations/Discussions on:

- the impact of RoHS regulations by industry experts
- the needs for standards for testing products and tools for declaring compositions/compliance of products

Proposed NIST Actions in response to consensus Industry requests:

- **CSTL** to work with IEC TC111 and ASTM to develop and validate test methods
- **CSTL** working on SRMs with certified values for restricted substances (Cr, Cd, Hg, Pb and Br flame retardants in polymers (with IRMM) and metals (brass and solder)).
- **EEEL** to work with IPC and IEC TC111 on declaration standards
- **MEP** to do outreach to SMBs nationwide
- **ITL** to coordinate with DoC ITA on interactions with other nations

How are We Managing the Load?

Increasingly, by providing measurement service delivery through collaborations with

- Private Sector (e.g., NTRMs)
- Other National Metrological Institutes (e.g. IRMM, LGC, NMI)
- Other U.S. Government Agencies
- More strategic partnerships like CARB and HML planned.



Relevance of measurement service delivery programs judged not only by NIST income but also by assessing impact of services as seen by Customer Sector

Program Selection and Evolution Case Study

Evolution of CSTL's Healthcare Measurements and Standards Program from Clinical Diagnostics to include:

- ***genomics***
- ***proteomics***
- ***Metabolomics***
- ***cell-based measurements***

NIST Linkages to Clinical Measurements Community

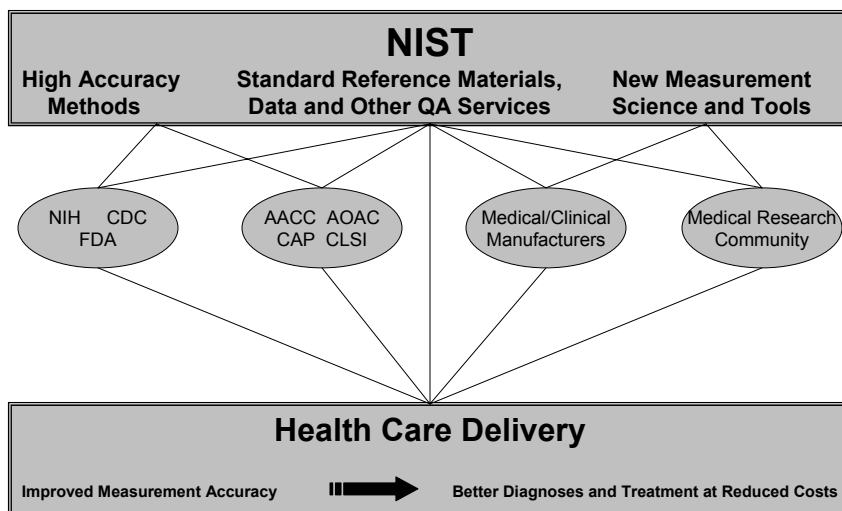
Program Guidance in setting priorities from:

- American Association for Clinical Chemistry (AACC)
- College of American Pathologists (CAP)
- Federal Agencies - NIH/CDC/NCI, FDA
- IVD Industry (e.g. Abbott, Beckman- Coulter, Roche)
- National Committee for Clinical Laboratory Standards (NCCLS)
- Joint Committee on Traceability in Laboratory Medicine (JCTLM)

AACC
Advancing
Clinical Laboratory
Science Worldwide



NIST's Role in Health Care Measurements



"the lack of organized measurement-related research can be best addressed by the coordinated efforts of NIST working together with industry"

-Health Industry Manufacturers Association

Heilmeier Questions

1. What is the problem, why is it hard?
2. How is it solved today and by whom?
3. What is the new technical idea; why can we succeed now?
4. Why should NIST do this?
5. What is the impact if successful and who would care?
6. How will you measure progress?

Prioritizing Via CSTL 5+1 Criteria

CSTL version of Heilmeier Questions

Industrial and/or National Need

The magnitude and immediacy of industrial and/or national need is assessed

Match to Mission

CSTL meets customer needs for measurements, standards, and data in the areas broadly encompassed by chemistry, biosciences, and chemical engineering

Contribution from CSTL Needed and will Make a Difference

CSTL's contribution is unique and critical for success

Nature and Size of Impact will be Noticeable

- The measure of anticipated impact relative to investment is evaluated (rate of return)
- Relevance of program judged by impact assessment not by income for NIST

Timely and Quality Output can be Provided

CSTL has the ability to respond in a timely fashion with high-quality output

Science/Technology Opportunity

Recent scientific and technological advances present new opportunities that warrant investigation

Measurements and Standards Impact Healthcare Costs and Quality of Life

Problem Magnitude and Scope:

U.S. Spends ~ \$1.8 trillion on Health Care

- ~10-15% of this amount is associated with measurement (>\$180B)
- Non-diagnostic measurements cost > \$40B

Costs of repeat measurements in Germany amounts to ~ 1.5 B US\$ per year – from German Health report 1998 (www.gbe-bund.de)

Measurement Bias Affects Quality of Life and leads to inefficiency in the application of new HC technologies

- Incorrect diagnosis and treatment
- Impairment of patient well-being
- Excessive and/or unnecessary costs



FISH DNA Test Detects Extra Copies of HER2 Gene in Breast Cancer Patients

Measurement Problem: Human Epidermal growth factor Receptor-2 (HER2) is a gene that is overexpressed in one-third of the 180,000 breast tumors diagnosed each year – the only tumors which respond well to treatment using very expensive Herceptin® therapy.

Results from HER2 assays both within and across platforms varied significantly, causing a large number of incorrect treatment prescriptions for many patients

Solution:

NIST is developing a cell-based SRM to benchmark FISH assays for HER2.

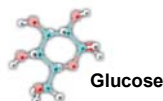
NIST has maintained Standards for 12 Health Status Markers for 20-years

Reference Systems are Currently in Place for Many Well-Defined Markers that are:

- Relatively small well-defined molecular or elemental species
- Typically, can be determined using well-established ID/MS –based methodology
- Such as the following:

<u>Marker</u>	<u>Disease State</u>
Calcium	Cancer, Blood Clotting
Chloride	Kidney Function
Cholesterol	Heart Disease
Creatinine	Kidney Function
Glucose	Diabetes
Lithium	Antipsychotic Treatment
Magnesium	Heart Disease
Potassium	Electrolyte Balance
Sodium	Electrolyte Balance
Triglycerides	Heart Disease
Urea	Kidney Function
Uric Acid	Gout
Vitamins	Nutrition Status

Demand for these SRMs have increased dramatically since the EU IVD Directive was implemented in December of 2003.



SRMs for Electrolytes and Metabolites

Examples include:

SRM 909b, Electrolytes and Metabolites in freeze-dried Human Serum

SRM 1951a Lipids in Frozen Human Serum

SRM 956 Electrolytes in Frozen Human Serum

SRM 965 Glucose in Frozen Human Serum

Certified for

Ca, Ca, Li, Mg, K, Na, Cl, cholesterol, creatinine, glycerides, triglycerides, urea, uric acid

Cholesterol, triglycerides (reference values for HDL-C and LDL-C)

Ca, Li, Mg, K, Na

Glucose



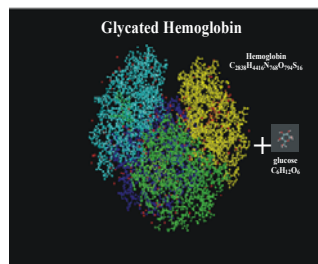
Sales of these SRMs have increased dramatically when the EU IVD Directive was implemented in December of 2003.

NIST has Expanded its Standards Program to Support New IVD Industry Needs

Reference Systems Being Developed for New Markers that typically exhibit:

- High molecular mass (>20,000 daltons)
- Heterogeneity of analyte
- Low concentration
- Instability of analyte form
- Cannot all be determined using ID/MS or other definitive methodologies
- Such as the following:

<u>Marker</u>	<u>Disease State</u>
Troponin-I	Myocardial Infarction
C-Reactive Protein	Risk of Heart Attack
Homocysteine	Risk of Heart Disease
Glycated Hemoglobin	Diabetes Status
T3, T4 and TSH	Thyroid Function
Speciated Iron	Hemochromatosis
PSA	Prostate Cancer
Cadmium & Mercury	Toxic Metal Poisoning
Folates	Neural Tube Defects
HER2	Breast Cancer
Fragile X	Mental Retardation



Drivers for NIST Activities:

- Standardization necessary before full medical diagnostic benefit can be realized
- IVD Industry needs
- Well-articulated US "Other-Agency" Needs (FDA, NCI, CDC etc)

Results of NCCLS-AACC Survey of Problem Analytes – 2001

Clinical laboratory personnel were asked to rate problem analytes based upon three criteria:

Inconsistent results between different methods
Results questioned by physician
Lot-to-lot shifts

Rank order from respondents:

- | | |
|--------------------|------------------------|
| 1. Troponin I | 7. Glycated Hemoglobin |
| 2. PSA | 8. Free T4 |
| 3. Glucose [POCT?] | 9. Bilirubin |
| 4. Creatinine | 10. Potassium |
| 5. Calcium | 11. <i>Amylase</i> |
| 6. <i>HCG</i> | 12. TSH |

In addition to its laboratory-based measurements and standards work, CSTL is providing leadership in Joint Committee on Traceability in Laboratory Medicine charged with:

Establishing the process for identifying, and reviewing against agreed upon criteria “higher order” Certified Reference Materials and Reference Measurement Procedures

Publishing a List of these “higher order” Standards required for IVD industry compliance with the EC IVD Directive regarding in vitro diagnostic medical devices.

Initially Published 1 April 2004, the Current List contains:

Reference Measurement Procedure entries for ~75 different health status markers **NIST has Reference Methods for 40**

Reference Material entries for ~130 measurands **NIST has Reference Materials for 80**

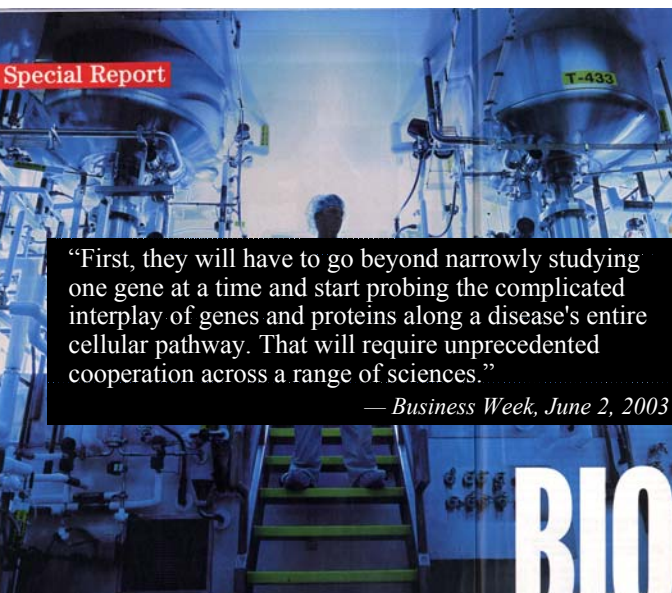
The List will be updated on an annual basis

Many additional Reference Methods and Materials need to be developed and the JCTLM is serving as an international forum have conducting needs Assessment and load sharing

07 Mar 2006; VCAT

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Looking to the future...



Special Report

“First, they will have to go beyond narrowly studying one gene at a time and start probing the complicated interplay of genes and proteins along a disease's entire cellular pathway. That will require unprecedented cooperation across a range of sciences.”

— *Business Week*, June 2, 2003

The science is hot and the stocks are up. Here's what's needed to deliver on the promise

BY ARLENE WEINTRAUB

Genentech's experimental colon cancer drug, Avastin, is anything but an overnight success. Thirteen years ago, one of its scientists found a gene that regulates blood flow in tumors, and started looking for a way to turn it off. It took the company five years to develop an antibody that could act as a switch in mice, and another three to fashion it into a drug. Then came animal tests, safety tests, and large-scale human trials to gauge the drug's effectiveness. And with every progress report, good and bad, Wall Street responded by pumping or withdrawing the company's shares.

Eight now, the pump is on. On May 18, Genentech Inc. announced that Avastin extends patients' lives when given with chemotherapy, ending hopes that it will be the first of a new class of drugs that can double off the supply of blood to tumors. Investors pushed Genentech's stock up 40%, to \$11, in the news. The trials aren't complete, and government approval isn't guaranteed, but Genentech is sanguine. “We're finding fundamentally different ways of treating people who are suffering and desperate,” says Genentech Chief Medical Officer Dr. Susan Dorrance Holmes.

Genentech-Holmes's optimism and her company's struggle with Avastin mirror the excitement of biotech across the board. Scientifically, the industry has reached a watershed: The human genome has been sequenced, so have the genomes of some microbes and animals. Every day, scientists learn more about the intricate molecular dance of life and how the process runs wild in disease. The technology to translate these discoveries into life-saving therapies also is advancing quickly.

The medical and commercial rewards in biotech are now abundantly clear. While it will take months for Avastin to reach the market, analysts believe it could eventually pull in more than \$1 billion a year. That would add significantly to the industry's revenue stream.

FIVE HURDLES FOR

BIOTECH

Genomics

sequencing the genome and measurements on genetic material

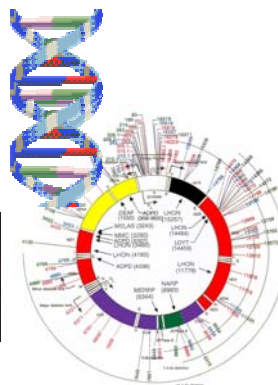
CSTL Role: Providing a Basis for Accuracy in DNA Measurements

Reference methods and standards for:

- *DNA-based Human identification*
- *Detection of DNA damage and repair*
- *Biomarkers for genetic diseases*

Since 1998 October 1, all federally-funded laboratories that conduct DNA testing must validate their procedures by using NIST SRMs.

Example:
New SRM 2395:
Y chromosome DNA markers



Proteomics

*... aims at the identification and quantitation of all proteins in a living system –
a map of all proteins that have been expressed by the genes*

*Proteomic technologies provide potential opportunities to solve **NCI mission-critical problems in cancer research**, such as:*

- *Sentinels for detecting cancer processes*
- *Targets for new therapeutics*
- *Biological markers of treatment response*

“In order for proteomics to be accepted as a valid science in clinical medicine, it is vital that the experimental results be reliable and reproducible within the scientific community.” -- Anna Barker, Deputy Director, NCI

NCI has requested that CSTL provide this community with “Well-characterized proteomic standards and reference materials ... needed to advance the field....
The absence of these standards and reference materials is a barrier to innovation ...and ... delays the discovery and transfer of proteomic technologies into clinical applications.”

In response to this need, CSTL has initiated a program to provide:

- *Reference methods and standards for individual proteins and simple mixtures*
- *Value-assigned complex mixtures of these proteins in plasma – first for use as measurement proficiency materials (for NCI grantee laboratories) and later as SRMs*
- *Reference mass spectra for peptides*

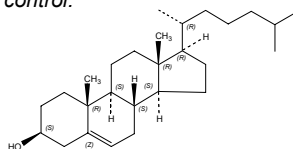
Metabolomics

Metabolites (small organic molecules) represent the end products of genetic expression. **Metabolomics** is the comprehensive analysis of large numbers of metabolites. These qualitative and quantitative relationships provide a holistic view of the biochemical status or biochemical phenotype of an organism.

NIH has requested that CSTL provide the community with:

A human plasma reference material value-assigned for 50 to 100 metabolites. This SRM will be used to:

- Compare procedures and equipment for their effectiveness in measuring different metabolites
- Identify most of the metabolites in a model biological system and their corresponding representations in multiple measurement platforms.
- Improve quantitative aspects of current and new technologies as they are developed.
- Improve reproducibility of measurements by providing a stable reference for comparison
- Provide a common reference sample that researchers can use for benchmarking, new methods development, and/or quality control.

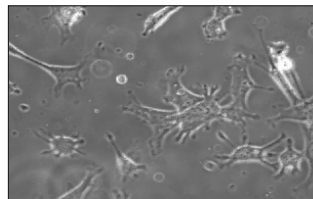


cholesterol

Cell-Based Diagnostics, Therapies, and Screening

- Cell-based diagnostics, therapies, and screening of new drug candidates is becoming big business.
- Efforts to quantify the response of cells is a new approach, and there is no infrastructure for such measurements.
- Work in **Academia** and by **Industry** not focussed on metrology
- Research efforts largely led by **Biologists** whose culture is to study observed phenomena qualitatively only

Cells are complex living systems; nature's smallest complete biological unit



A quantitative understanding of the physical and chemical processes that cause observed biological response and function will facilitate innovation in this area. **NIST Measurements and Standards are essential for success**

A Vision for CSTL

CSTL is seen by its staff and stakeholders as providing value to our customers with the *right measurements and standards at the right time.*

We succeed by:

- *Identifying our customer needs in an open and consistent process.*
- *Understanding, anticipating and responding cost-effectively to customer needs.*
- *Balancing research and services, projects and people, and new and existing strengths, skill sets, and expertise.*
- *Working collaboratively and in partnership to leverage resources for the best strategic and stakeholder outcomes.*
- *Advancing the fundamental science basis for global measurement systems.*
- *Consistently assessing the value and impact of our work.*



**For further
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**or visit us at
www.cstl.nist.gov**